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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/973,375	10/09/2001	Donald Gerald Stein	07157/239838 (5543-17)	5877

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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
05/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/973,375	STEIN ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C: § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *1-12, 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the response filed by the applicant on 02/20/2007.

Applicant's arguments have been fully considered, but not found persuasive, the rejection of claims 1-12, and 15-20 under 35 U.S.C. 103(a) as being unpatentable over Roof et al., (*Molecular and Chem. Neuropathology*, 1997, vol.31, 1-11, of record), in view of Backstrom et al. (US 6,455,516, PTO-892), and Gee et al. (Re. 35,517, of record) is MAINTAINED. See under response to the arguments.

Applicant's arguments have been fully considered, but not found persuasive, the rejection of claims 1-12, and 15-20 under 35 U.S.C. 103(a) as being unpatentable over Roof et al. (*Restoration Neurology and Neuroscience*, 1992, vol.4, 425-427, of record), in view of Backstrom et al. (US 6,455,516, PTO-892), and Gee et al. (Re. 35,517, of record) is MAINTAINED. See under response to arguments

Applicant's arguments have been fully considered, but not found persuasive, the rejection of claim 14 under 35 U.S.C. 103(a) as being unpatentable over Roof et al. in view of Backstrom et al. (US 6,455,516, PTO-892), and Gee et al. (Re. 35,517, of record) as applied to claims 1-12, and 15-20 above, and further in view of Weinshenker et al. (5,068,226) is MAINTAINED.

Currently, claims 1-12 and 14-20 are pending in this application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12, and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roof et al., (*Molecular and Chem. Neuropathology*, 1997, vol.31, 1-11, of record), in view of Backstrom et al. (US 6,455,516, PTO-892), and Gee et al. (Re. 35,517, of record).

Roof et al. discloses that progesterone has been shown to have neuroprotective effects following traumatic brain injury in rat patients, and/or in injured nervous system including the severity of postinjury cerebral edema in rat patients. See the entire article especially abstract and introduction.). It is also disclosed that postinjury cerebral edema causes substantial cell loss. See page 2. Roof et al. particularly discloses the administration of progesterone to male rat patients after suffering medical frontal cortex contusions, i.e., initial treatment of progesterone with a pharmaceutical carrier, oil, by injection, 4 mg/kg, was given 5 min post-injury and the remaining injections, 4 mg/kg, were given 6 hour post-injury and again once each 24-hours (see the last paragraph of page 3 to page 4 the 3rd paragraph), or the initial treatment after injury occurs at least within 2 hours of contusion (see page 6-7). Roof et al. also teaches that other agents or compounds such as vitamin E and methylprednisolone are known to be useful in the

claimed method with progesterone (see page 3, lines 5-9). It is also disclosed that postinjury cerebral edema causes substantial cell loss. See page 2.

Note that Roof et al. discloses that the effective amount of progesterone to be administered is in the range of 4 mg/kg, which is the instant claimed amount in claim 8 herein and also within the claimed effective amounts, about 1 μg/kg- 50 mg/kg, in claim 7 herein.

Roof et al. does not explicitly teach the administration of progesterone metabolite, allopregnanolone for the treatment methods therein.

Backstrom et al. teach that allopregnanolone is a progesterone metabolite, which is useful for treating CNS disorders

Gee et al. discloses that progesterone metabolites including the particular progesterone metabolite, allopregnanolone, are useful in a method for treating seizure disorders in a patient in need thereof (see particularly col.4 lines 37-39; col.1 lines 17-21; Table 2 at col.13-14). Gee et al. also discloses that the beneficial effect of progesterone is related to the conversion of progesterone to the active metabolites including allopregnanolone since the metabolites and derivatives possess higher potency and efficacy than progesterone (see col.17 lines 29-35).

It would have been obvious to a person of ordinary skill in the art at the time of invention to administer allopregnanolone for treating traumatic central nervous system injury because 1) Roof et al. teach that progesterone is known to have neuroprotective effects in injured nervous system following traumatic brain injury in rat patients, and/or in injured nervous system including the severity of postinjury cerebral edema in rat

patients, 2) allopregnanolone is a progesterone metabolite which is well known to be useful for treating CNS disorders according to Backstrom, and 3) Gee et al. teaches that allopregnanolone possess higher potency and efficacy than progesterone.

Thus, one of ordinary skill in the art at the time of invention would have motivated to administer progesterone metabolite, allopregnanolone with reasonable success of treating traumatic central nervous system injury associated disorders with superior efficacy and potency than progesterone.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12, and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roof et al., Roof et al. (*Restoration Neurology and Neuroscience*, 1992, vol.4, 425-427, of record), in view of Backstrom et al. (US 6,455,516, PTO-892), and Gee et al. (Re. 35,517, of record).

Roof et al. discloses that progesterone is useful in treating brain edema resulting from traumatic brain injury or following contusion injury in male and female rat patients. See the entire article especially abstract and introduction. Roof et al. particularly discloses the administration of progesterone with a pharmaceutical carrier, peanut oil, to

male rat patents after suffering medical frontal cortex contusions, i.e., initial treatment of progesterone by injection, 4 mg/kg, was given 1 hour after contusion and the remaining injections, 4 mg/kg, were given 6, 24 and 48 hour post-injury (see the 3rd paragraph of page 426), or the initial treatment after injury occurs at least within 2 hours of contusion (see page 6-7).

Note that Roof et al. discloses that the effective amount of progesterone to be administered is in the range of 4 mg/kg, which is the instant claimed amount in claim 8 herein and also within the claimed effective amounts, about 1 μg/kg- 50 mg/kg, in claim 7 herein.

Roof et al. does not explicitly teach the administration of progesterone metabolite, allopregnanolone for the treatment methods therein.

Backstrom et al. teach that allopregnanolone is a progesterone metabolite, which is useful for treating CNS disorders

Gee et al. discloses that progesterone metabolites including the particular progesterone metabolite, allopregnanolone, are useful in a method for treating seizure disorders in a patient in need thereof (see particularly col.4 lines 37-39; col.1 lines 17-21; Table 2 at col.13-14). Gee et al. also discloses that the beneficial effect of progesterone is related to the conversion of progesterone to the active metabolites including allopregnanolone since the metabolites and derivatives possess higher potency and efficacy than progesterone (see col.17 lines 29-35).

It would have been obvious to a person of ordinary skill in the art at the time of invention to administer allopregnanolone for treating traumatic central nervous system

injury because 1) Roof et al. teach that progesterone is known to have neuroprotective effects in injured nervous system following traumatic brain injury in rat patients, and/or in injured nervous system including the severity of postinjury cerebral edema in rat patients, 2) allopregnanolone is a progesterone metabolite which is well known to be useful for treating CNS disorders according to Backstrom. Furthermore, Gee et al. teaches that allopregnanolone possess higher potency and efficacy than progesterone.

Thus, one of ordinary skill in the art at the time of invention would have motivated to administer progesterone metabolite, allopregnanolone with reasonable success of treating traumatic central nervous system injury associated disorders with superior efficacy and potency than progesterone.

Response to Arguments

Applicant argues that "Backstrom et al. teach the use of epiallopregnanolone (3β-hydroxy-5α-pregnan-20-one) for the treatment of steroid-induced CNS disorders, including disorders caused by allopregnanolone (3α-hydroxy-5α-pregnan-20-one) (See, e.g., Backstrom et al. column 1, lines 14-23 and column 3, lines 20-29). In other words, the Backstrom et al. reference actually teaches away from its combination with the other cited references. Backstrom et al. teach that allopregnanolone is a sedative compound that can cause disorders such as epilepsy, depression, and stress; the same disorders for which Gee et al. teach the administration of allopregnanolone as a treatment (See, e.g., Backstrom et al. column 3, lines 20-29, column 6". This argument has been considered, but not found persuasive because 1) Backstrom et al. reference was employed for its teachings that allopregnanolone is a progesterone metabolite, and 2)

Backstrom et al. teach that allopregnanolone (3α-hydroxy-5α-pregnan-20-one) can be used as anti-epileptic substance (see column 1, lines 48-49) i.e can be used for treating seizure, and Gee et al. also teach that allopregnanolone is useful in a method for treating seizure. Thus, there is clear motivation to combine the cited prior art.

Applicant argues that "Gee et al. does not teach or suggest that allopregnanolone would have higher potency and efficacy in the treatment of different disease states such as in patients following a traumatic injury to the CNS as instantly claimed." This argument has been considered, but not found persuasive because Gee et al. discloses active progesterone metabolite, allopregnanolone possess higher potency and efficacy than progesterone in treatment of seizures. Even though Gee et al. does not teach the superior efficacy of allopregnanolone for instant specific diseases, it has been well-established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the art, to person of ordinary skill in the art. In re Boe, 355 F.2d 961, 148 USPQ 507, 510 (CCPA 1966); In re Lamberti, 545 F.2d 747, 750, 192 USPQ 279, 280 (CCPA 1976); In re Fracalossi, 681 F.2d 792, 794, 215 USPQ, 570 (CCPA 1982); In re Kaslow, 707 F.2d 1366, 1374, 217 USPQ 1089, 1095 (Fed. Cir. 1983). Further, note that seizures are known to be resulted from traumatic brain injury (see Hernandez et al., Seizures, epilepsy, and functional recovery after traumatic brain injury: a reappraisal, of record). Thus, from the teachings of Gee et al., one of ordinary skill in the art at the time of invention would have motivated to administer progesterone metabolite,

allopregnanolone with reasonable expectation of treating traumatic central nervous system injury associated disorders with superior efficacy and potency than progesterone.

Applicant argues that "various progesterone metabolites have been found to exhibit divergent and conflicting mechanisms of action compared to progesterone and to each other (See parts 4(c)(i)-(iv) of the declaration of Dr. Wright filed on December 19, 2003). Accordingly, one of skill in the art would not have had a reasonable expectation of success in the substitution of allopregnanolone for progesterone in the methods of Roof et al. based on the findings of Gee et al. relating to seizure disorders or the teachings of Backstrom et al. that allopregnanlone causes steroid-induced CNS disorders". This argument has been considered, but not found persuasive as discussed above. Further, the declaration of Dr. David W. Wright under 37 CFR 1.132 has been fully considered but is ineffective to overcome the 103(a) rejections herein as to nonobviousness over the prior art, since the declaration merely presents Dr. Wright's opinion or statements or conclusion regarding the claimed treatment herein and the cited prior art, but fails to set forth any factual evidences. Note that arguments of counsel cannot take the place of factually supported objective-evidence, See, e,g., In re Huang, 100F,3d135,-139-40, 40USPQ2d 1685, 1689 (Fed. Cir. 1996); In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191,196 (Fed. Cir. 1984).

Thus, as discussed above, Allopregnanolone is known to possess higher potency and efficacy than progesterone according to Gee et al. Therefore, one of ordinary skill in the art would have expected with a reasonable success that the

particular progesterone metabolite, allopregnanolone, would be useful in a method for treating a traumatic central system injury and a method of decreasing neurodegeneration in a subject following a traumatic injury to CNS, because of having the same therapeutic usefulness as progesterone in CNS and even exhibiting higher potency and efficacy, compared to progesterone, absent evidence to the contrary.

Applicant argues that "this obviousness rejection amounts to hindsight reconstruction of the claimed invention. None of the cited references would guide one of skill in the art to select allopregnanolone from among the multitude of progesterone metabolites and administer this compound to a patient identified as having a traumatic central nervous system injury." This argument has been considered, but not found persuasive as discussed above. Further in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Roof et al. in view of Backstrom et al. (US 6,455,516, PTO-892), and Gee et al. (Re. 35,517, of record) as applied to claims 1-12, and 15-20 above, and further in view of Weinshenker et al. (5,068,226).

Roof et al. in view of Backstrom et al. and Gee et al. is as discussed above.

The prior art does not expressly disclose the employment of cyclodextrin as the carrier for the particular progesterone metabolite, allopregnanolone.

Weinshenker et al. discloses that cyclodextrins are broadly known to be useful as carriers for improving the delivery of active agents such as steroids, e.g., cyclodextrins enhancing the solubility of progesterone 2000 fold and similar effects are observed with other steroids such as prednisolone (see col.6 lines 20-32).

One having ordinary skill in the art at the time the invention was made would have been motivated to employ cyclodextrin as the carrier for the particular progesterone metabolite, allopregnanolone since that cyclodextrins are broadly known to be useful as carriers for improving the delivery of active agents such as steroids, e.g., cyclodextrins enhancing the solubility of progesterone 2000 fold and similar effects are observed with other steroids such as prednisolone according to Weinshenker et al.

Response to Arguments:

Applicant's arguments have been considered, but not found persuasive as discussed above.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Tuesday, Thursday-Friday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni, Ph.D
Patent Examiner
Art Unit : 1617

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER